

### REMARKS

Applicant respectfully requests reconsideration. Claims 1-10, 24, 36, 51 and 95-111 were previously pending in this application. Claims 1, 24, 36 and 106 are amended herewith. Claim 105 has been canceled. New claims 112-118 have been added. Support for the claim amendments and newly added claims can be found in the instant specification on, for example, page 4, line 11; page 5, lines 5-8; page 10, lines 8-10; page 15, lines 17 and 29-32; page 32, lines 19-21; page 36, lines 21-26 and in the claims as originally filed. Therefore, claims 1-10, 24, 36, 51, 95-104 and 106-118 are currently pending with claims 1, 24, 36, 51, 112, 114 and 118 being independent claims. No new matter has been added.

### Election/Restriction

In regard to the Examiner's comment that "The group of inventions lack unity because Urry (US 4,589,882) disclose the claimed special technical feature, the attachment of a tissue to an agent by lysyl oxidase cross-linking.", Applicant does not concede that the Examiner's conclusion regarding the disclosure of Urry or unity of invention is in fact correct.

### Rejections under 35 U.S.C. §112

The Examiner rejected claims 8-10, 36, 102 and 103 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner has rejected claims 8 and 9 for reciting "complementary linker", claim 36 for reciting "an isolated form" and claims 10, 102 and 103 for reciting "rich".

Applicant respectfully traverses this rejection. Not only would one of ordinary skill in the art understand the meaning and scope of the terms based on their plain meaning in the context of the language of the rejected claims, but the specification provides definitions for each. Therefore, one of ordinary skill in the art would certainly understand what Applicant regards as the claimed invention.

On page 6, lines 12-13, of the specification, the term "complementary" is defined. The definition provides that complementary molecules are molecules that can be covalently joined. It follows that a complementary linker is a linker that can covalently bind to another linker, and in

the context of the rejected claims this other linker is a substrate of lysine oxidase or a compound that reacts with lysine oxidase products. Therefore, a complementary linker in the context of the rejected claims is one that can covalently bind to linkers that possess an amine, aliphatic amine, lysine and/or aldehyde. Examples of such complementary linkers, while not necessary to satisfy the definiteness requirement, are provided on page 6, lines 1-2, and include polymers rich in lysine or both glutamine and lysine.

On page 32, lines 11-18, the term “isolated” is defined. The specification provides that isolated means that the material is essentially free of other substances to an extent practical and appropriate for the intended use of the material. For example, in the case of pharmaceuticals and cosmetics, the materials are likely to be substantially pure. In the case of proteins, the proteins are sufficiently pure and sufficiently free from other biological constituents of the host cells from which the proteins are derived so as to be useful in the methods according to the invention. Such a definition is sufficient to make the use of the term in the context of the rejected claims sufficiently clear to one of ordinary skill in the art.

Finally, on page 15, lines 30-32, the meaning of “rich in lysine” in reference to a polymer and consistent with the language of the rejected claims is provided. The definition provided clearly indicates that a polymer rich in lysine is a molecule wherein at least 20% of the units of the polymer are lysine, or wherein the molecule includes at least 3 contiguous, linked lysines.

Therefore, based on the plain meaning of the terms as well as the definitions and examples provided in the instant specification, one of ordinary skill in the art would certainly understand the meaning and scope of the terms as recited in the rejected claims.

Accordingly, withdrawal of this rejection is respectfully requested.

#### Rejections Under 35 U.S.C. §102

The Examiner rejected claims 1-3, 8-10, 24, 96-106, 108 and 109 under 35 U.S.C. §102(e) as allegedly being anticipated by Stedronsky, in light of Webster's Dictionary. The Examiner argues that Stedronsky teaches the attachment of an agent to a body tissue via a linker by crosslinking with lysyl oxidase.

Applicant respectfully disagrees. Stedronsky involves adhesives that are cross-linkable to one another using, for example, enzymes such as lysyl oxidase. Stedronsky purports to

improve the use of such adhesives with the use of primer molecules that are capable of interacting with native components, such as proteins, in tissue. Examples of these primer molecules include chaotropic agents, dyes, aliphatic sulfonates, aromatic or aliphatic sulfates, phosphates, carboxylates and mammalian proteins. Applicant notes that column 3, lines 1-5, of Stedronsky, which was cited by the Examiner, indicates that the primer molecules can be dyes capable of staining tissue-associated proteins, such as collagen, actin, myosin, etc. This passage, however, does not indicate that the primer molecules are such tissue-associated proteins. Stedronsky teaches that the primer molecules, for example, disrupt the hydrogen bonding, alter the electrostatic nature, alter the hydrophobic nature, alter the degree of hydration, or alter the density and/or degree of openness of native component(s) in tissue. The activity and interaction of the primer molecules with tissue, however, does not require any enzyme. The methods of Applicant's rejected claims are quite different from these teachings.

For example, claim 1 of the instant application, is directed to attaching a conjugate of an agent and a linker to a tissue with lysine oxidase. Unlike Stedronsky, the enzyme acts on the linker (allegedly the primer in Stedronsky) and the tissue. Stedronsky does not teach that a linker is attached to tissue with lysine oxidase. The lysyl oxidase mentioned by Stedronsky is for use in crosslinking the adhesive/sealant itself (for the formation of the tissue adhesive) and not for attaching a linker to tissue. Column 8, lines 33-41, cited by the Examiner does not describe crosslinking of a primer to tissue but rather crosslinking of the adhesive components to each other to form the adhesive. Therefore, Stedronsky does not teach the attachment of an agent to a tissue via a linker by crosslinking with lysyl oxidase as the Examiner has asserted. In addition, as stated above, claim 1 is directed to attaching a conjugate of an agent and a linker. Stedronsky does not teach the application of such a conjugate to tissue.

Claim 24 is directed to attaching an agent to tissue by first attaching a linker to the tissue, and then applying to the tissue an agent that is a substrate of lysine oxidase together with lysine oxidase so that the linker and agent are covalently bonded. Stedronsky, however, does not provide that the linker and agent are covalently bonded with the use of lysine oxidase, as the enzymatic crosslinking with lysyl oxidase provided in Stedronsky only refers to crosslinking the adhesive/sealant to form the adhesive.

In regard to claim 51, which Applicant believes the Examiner intended to be included in the rejection, Applicant notes that the Examiner on page 4 of the Office Action states that the adhesive/sealant satisfies the limitation of instant claim 101 in that it does not comprise a microparticle. However, in regard to the apparent rejection of claim 51, the Examiner argues the opposite (i.e., that the polymers of the tissue sealant are allegedly comprised of “particles”). The Examiner cannot in one instance assert that the tissue sealant is comprised of microparticles and in another that it is not. It is not clear to Applicant which logic the Examiner would like to follow. Applicant maintains that the teachings of Stedronsky do not provide attaching microparticles to a skin surface by crosslinking of the microparticles to the skin with lysine oxidase.

Finally, Applicant notes that the Examiner has not demonstrated how the primer molecules of Stedronsky are rich in lysine according to the definition provided in the instant specification.

Applicant maintains that the teachings of Stedronsky are insufficient to support an anticipation rejection. In order for a reference to be anticipatory it must teach all of the elements of a rejected claim. As Stedronsky does not teach at least the features of the claims as described above, Applicant maintains that Stedronsky fails to anticipate the rejected claims.

Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner rejected claims 36 and 107 under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 4,589,882 to Urry.

While Applicant does not concede the correctness of the Examiner’s rejection, Applicant has amended claim 36. Therefore, Applicant believes this rejection is now moot.

Accordingly, withdrawal of this rejection is respectfully requested.

#### Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1-10, 24 and 95-106 under 35 U.S.C. §103(a) as being allegedly unpatentable over Stedronsky, as applied to claims 1-3, 8-10, 24 and 96-104 in view of U.S. Patent No. 6,010,871 to Takahara et al.

Applicant again respectfully disagrees. As discussed above, Applicant maintains that Stedronsky does not provide the methods of Applicant's rejected claims. For example, Stedronsky fails to provide the attachment of a conjugate of an agent and linker to a tissue or the attachment of an agent to a linker or a linker to tissue with lysine oxidase. The use of lysyl oxidase provided in Stedronsky is quite different than what is represented in the methods of the rejected claims. Again, the lysyl oxidase mentioned by Stedronsky is for use in crosslinking the adhesive/sealant itself for the formation of the tissue adhesive. The teachings of Takahara do not remedy this by providing the teachings absent in Stedronsky. Takahara uses polylysine to improve the *in vivo* residence time and reduce the antigenicity of a pharmaceutical agent when administered *in vivo*. Takahara does not teach administering a conjugate of an agent and linker to tissue or the use of lysine oxidase to attach a linker to tissue or a linker to an agent. Therefore, on this basis alone, the references fail to provide the methods of Applicant's rejected claims, and the obviousness rejection fails.

Additionally, the references fail to sustain an obviousness rejection as there is no motivation to combine them (to replace the primers of Stedronsky with the polylysine of Takahara) and there is no demonstrated expectation of success in doing so. Neither the teachings of Stedronsky or Takahara would lead one of ordinary skill in the art to use polylysine in place of the primers of Stedronsky. Stedronsky provides primers for use in improving the performance of tissue adhesive/sealant systems. The primers are intended to alter the physical characteristics of the tissue components such that an improvement in the mechanical performance of a tissue adhesive/sealant is achieved. The activity and interaction of the primers with tissue does not require lysine oxidase. Takahara, on the other hand, uses polylysine to improve the *in vivo* residence time and reduce the antigenicity of a pharmaceutical agent when administered *in vivo*. This is quite different from the use of the primers of Stedronsky, and contrary to the Examiner's assertions, there is no demonstration that polylysine could serve as a primer as intended by Stedronsky or that one of ordinary skill in the art would think that polylysine could be so used.

Applicant believes that this rejection and the combination of these references was made with the use of hindsight based on Applicant's instant disclosure. Such hindsight is impermissible. Knowledge of the Applicant's disclosure must be put aside, and only facts from

the prior art may be used to support an obviousness rejection. Applicant maintains such facts have not been provided.

Accordingly, withdrawal of this rejection is respectfully requested.

#### Double Patenting Rejection

The Examiner rejected claims 1-10, 24, 36, 51 and 95-108 under the judicially created doctrine of obviousness-type double patenting, as being allegedly unpatentable over claims 1-46 and 48 of U.S. Patent No. 6,267,957 in view of U.S. Patent No. 6,258,872 to Stedronsky and Webster's Dictionary.

Applicant respectfully disagrees. The claims of U.S. Patent No. 6,267,957 are directed to attaching agents to tissue via a linking molecule in the presence of transglutaminase. Applicant maintains that it is not obvious for one of ordinary skill in the art to attach agents to a body tissue with lysine oxidase in light of Stedronsky as the Examiner has argued. Again, the lysine oxidase of Stedronsky is used to crosslink the adhesive/sealant but not to attach an agent to a linker or a linker to a body tissue. Stedronsky does not provide that attachment to tissue can be performed with any enzyme. In fact, Stedronsky teaches that attachment to tissue requires the use of primer molecules which alter characteristics of the tissue. The primer molecules of Stedronsky interact and alter tissue without requiring enzymes, such as lysine oxidase. Therefore, it would not be obvious for one of ordinary skill in the art to use lysine oxidase in place of transglutaminase to attach agents to tissue based on the teachings of Stedronsky.

Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner provisionally rejected claims 1-10, 24, 36, 51 and 95-108 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 1-52 of copending Application No. 11/144372 in view of Stedronsky and Webster's Dictionary.

The Examiner has raised a provisional double patenting rejection based on a copending unallowed application. For the same reasons set forth above, Applicant maintains that the claimed invention is not obvious over the cited prior art, and, therefore, Applicant submits that the double patenting rejection does not apply. In view of the unallowed state of the copending

application, however, Applicant maintains the right to further address this rejection in the event the rejection is maintained and does not at this time wish to file a terminal disclaimer.

Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner provisionally rejected claims 1-10, 24, 36, 51 and 95-111 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 1-50 of copending Application No. 11/125830 in view of Stedronsky.

The Examiner has raised a further provisional double patenting rejection based on a copending unallowed application. Again, for the same reasons set forth above, Applicant maintains that the claimed invention is not obvious over the cited prior art, and, therefore, Applicant submits that the double patenting rejection does not apply. In view of the unallowed state of the copending application, however, Applicant maintains the right to further address this rejection in the event the rejection is maintained and does not at this time wish to file a terminal disclaimer.

Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner provisionally rejected claims 1-10, 24, 36, 51 and 95-108 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 22, 25, 145-152, 155, 156, 158-165 and 167-173 of copending Application No. 09/620783 (now allowed) in view of Stedronsky.

Applicant notes that Application No. 09/620783 has been patented as U.S. Patent No. 6,958,148. The claims of this patent are directed to the attachment of microparticles to tissue with transglutaminase. Again, as provided above, Applicant maintains that the teachings of Stedronsky do not make obvious the use of lysine oxidase for crosslinking to tissue.

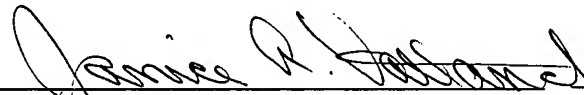
Accordingly, withdrawal of this rejection is respectfully requested.

**CONCLUSION**

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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